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(54) A METHOD OF MAKING GRANULES

(71) We, KLINGE PHARMA GMBH & CO., formerly known as Chemisch-pharmazurtische Fabrik, Adolf Klinge & Co., a German Company of 8 Munchen 40, Leopoldstrasse 16, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Powder materials, in particular therapeutically active substances, are granulated in order to be brought into a state which is more suitable for processing into tablets. Generally, materials are processed into granulates by adding a granulating liquid to the pulverized material in connection with vigorous stirring and mixing, so that the powder particles are agglomerated and glued together into granules. The granulating liquid may consist of an aqueous solution of a water-soluble substance, e.g. a solution of sugar, or it may consist of a solution of a water-soluble binder, e.g. a natural rubber or a soluble cellulose derivative. Instead of aqueous solutions one may also employ organic solutions of readily vaporizable liquids, in particular alcoholic solutions of such binders, in which connection the liquid must in any case be evaporated after the processing and granulation, in order to obtain products that can be processed further in the dry state. It is also known to form granulate grains by fixing the pulverized effective substance on small neutral cores. Also in this case one works in a mixer while using a granulating liquid, the powder to be applied to the cores being added gradually while the granulating liquid is admixed. The granulation by means of the granulating liquid can be attained not only through mechanical stirrers but also by mixing the material to be granulated with the granulating liquid in a fluidized bed, in which manner the granulation and drying of the obtained granulate are attained in a single operation.

German Offenlegungsschrift 2,127,683, describes a process of preparing granulates, wherein a binder, which melts or softens at a temperature which is not detrimental to the active substance, is admixed with the powder of active material or the powder mixture to be later processed into tablets. After the admixture, the material is warmed up in a fluidized bed above the melting point of the binder and then again cooled below the melting point of the binder without interrupting the air flow through the fluidized bed. As binders one may use in this connection physiologically acceptable waxes, fats, polyalkyleneglycols or other solid substances that melt or soften between 40 and 100°C. The binder is finely comminuted and added to the active substance and then heated in the air flow.

German Offenlegungsschrift 2,123,513, relates to a process for fluidized granulation of powder-type pharmaceutical components, the pulverised main component of the mixture is agglomerated within the fluidized bed to an inert pulverised plasticized sinter component, which is plastic at a temperature that is situated below the critical temperature of the main component to be embedded. Also in this known process the material must be warmed up by means of a hot flow of air.

We have now unexpectedly found that granulates can be obtained very rapidly and simply by processing a pharmaceutically active powder material of the granulate together with a fusible binder material in a fluidizing mixer. The present invention accordingly provides a process for manufacturing granulates which comprise dry working a mixture of a pulverized pharmaceutically active and pharmaceutically acceptable fusible material in a fluidizing mixer at a temperature not substantially above the melting point respectively of the binder material.

The term "fluidizing mixer" used herein refers to a known type of mixer in which the material to be mixed is agitated mechanically, usually by a rotating rod,

blade or propellor, sufficiently to fluidize the mixture. The mechanical energy expended being sufficient to cause substantial temperature rise in the material being mixed. The term does not refer to fluidized bed mixers in which the materials to be mixed are fluidized by passage of a fluid and wherein the temperature is determined by the fluidizing fluid.

The use of the fluidizing mixer, especially without a heat supply from outside, provides a gentle warming of the material such that the temperature generally does not rise above the melting point of the binder material and yet the agglomeration of the powder materials into a granulate proceeds readily. This novel process provides the possibility of rapidly processing a very great variety of pharmaceutically active materials into the form of a granulate. Examples include lactose or medicaments, and in particular pharmaceutically active substances that are very sensitive to temperature. The granulates may then be used for the preparation of tablets and similar forms of preparation. When the pulverized mass consisting of the pharmaceutically active substance and pulverized fusible binder material is processed in the fluidizing mixer, the impacts and shear action exerted on the powder particles of the binder material produce a local warming of the surface so that the particles of the embedding material become plastic and adhesive on the surface, without the requirement of providing external energy to heat the entire mixture up to or above the melting temperature of the embedding material such as happens in the fluidized bed process of the prior art.

The fluidizing mixer can be operated as closed apparatus and therefore the process of the invention can be carried out under a protective gas or *in vacuo*.

Since the dry agglomeration of the powder material into granulate in the fluidizing mixer is effected very rapidly, it is possible with a given apparatus to process gently substantially larger amounts of material than it was possible until the present time while using a suitable vortex-type impeller mixing apparatus.

Fusible binder materials suitable for use in the process of the invention include especially the physiologically-compatible fats, fatty alcohols, waxes, polyalkylene glycols, etc. For certain purposes in place of binder materials that are not soluble in water, it is possible to use water-soluble binder materials, in order to obtain a faster rate of physiological dissolution of the granulates or of the tablets produced therefrom.

Those skilled in the art can readily see that the novel principle of preparing granulates in a fluidizing mixer can be readily adapted to the special requirements of the granulate processing. Modification is readily possible by adding various auxiliary, flavouring and similar materials.

The novel process of preparing granulates is explained more in detail in the following text by means of a few examples.

Example 1

24.8 g of sodium fluoride and 1475.2 g of stearyl alcohol are mixed and agglomerated under compression in a Henschel fluidizing mixer FM 10 for 5 minutes while the powder mixture warms up to 59°C. After cooling down, the granulate fraction having the particle diameter of 0.6 to 1.25 mm, which is particularly suitable for the making of tablets, is separated by sieving the material first through a sieve having a mesh width of 1.5 mm, and subsequently separating the undersize grain smaller than 0.6 mm.

Example 2

1200 g of cetylstearyl alcohol and 200 g of caffeine are mixed and compressed in the Henschel fluidizing mixer FM 10 until the temperature reaches the softening temperature of the cetylstearyl alcohol at 48°C. The final point of the granulation process could readily be detected from the rapidly increasing current consumption of the fluidizing mixer motor. The screen analysis of the obtained granulate produced a yield of 68% in the grain-size range of 0.75 to 1.35 mm.

Example 3

9750 g of horse-chestnut powder extract, containing 18.2% escin, 145 g of aneurin mononitrate, 3510 g of polyglycol ether (molecular weight 6000), 4167 g of lactose and 470 g of magnesium stearate are dry-granulated according to the procedure of the invention in the Henschel fluidizing mixer FM 75. The mixing time was about 5 minutes, in which connection it was noted that the temperature increased up to 75°C. After cooling down, the material is sieved by means of a sieve having a mesh width of 1.2 mm. The granulate is ready for pressing and may immediately be worked into tablets. The following grain distribution was determined:

100—500μ 21%
500—800μ 55%
800—1200μ 24%

Example 4

4000 g of nicotinic acid, 8000 g of oxyethyltheophylline, 4400 g of horse-

chestnut, extract, containing 18.2% escin, 2880 g of polyglycol ether (6000), 320 g of magnesium stearate were processed as described in Example 3 and worked into a granulate that can be readily pressed into tablets.

Example 5

In order to produce a granulate for hormone pills, a mixture was made from 1256 g of suger powder and 200 g of polyglycol ether (6000), which mixture was worked for about 15 minutes in the fluidizing mixer FM 10 during which time the temperature rises to 65°C. Then, 15.5 g of sodium oestrone sulfate (60.6%) were introduced and the granulation was performed for a further 2 minutes in the closed apparatus. The granulate of 0.1 to 1 mm in size could be pressed directly into pill cores.

Example 6

7500 g of α-escin-sodium, 6000 g of lactose and 3500 g of polyglycol ether (6000) are introduced to be worked in the Henschel fluidizing mixer FM 75 and agglomerated for 4 minutes during which time the temperature rises to 65°C. After screening through a sieve of 1 mm mesh width, one obtains a granulate ready for pressing. The fine fraction below 100μ at most 5%.

Example 7

10000g of acetyl salicylic acid plv. subt. (90% smaller than 50μ), 10000 g of phenacetine plv. subst. (90% smaller than 50μ), 2000 g of codeine 1200 g of maize starch, 140 g of sodium lauryl sulfate and 2400 g of stearic acid (total amount: 25.74 kg) are mixed and agglomerated together in a Henschel fluidizing mixer FM 75 until the temperature reaches 70°C. After cooling, the granulate was passed through a sieve, mesh width 1.5 mm. In order to increase the rate of dispersal of the embodying material 2.2 g of potato starch was admixed while using a gentle-action stirrer ordinarily used in such cases. The obtained granulate mixture could be pressed into hard tablets with high accuracy of dosage at relatively low pressure on high-capacity rotary presses, without exhibiting any tendency for the tabletting composition to stick to the press or for newly formed tablets to fracture on release of pressure in the press.

WHAT WE CLAIM IS:—

1. A process for manufacturing granulates which comprises dry working a mixture of a pulverized pharmaceutically active material and a pharmaceutically acceptable fusible binder material in a fluidizing mixer as herein before defined at a temperature not substantially above the melting point respectively of the binder material.

2. A process as claimed in Claim 1 wherein no heat is supplied to the process from an external source.

3. A process as claimed in either Claim 1 or Claim 2 wherein the process is carried out under a protective gas or in vacuo.

4. A process as claimed in any one of Claims 1 to 3 wherein the binder material is one or more physiologically compatible fats, fatty alcohols, waxes or polyalkylene glycols.

5. A process as claimed in any one of Claims 1 to 4 and substantially as hereinbefore described.

6. Granular materials whenever fabricated by the process claimed in any one of Claims 1 to 5.

7. Tablets whenever made from the granular material claimed in Claim 6.

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